

LCR is a component of the β -globulin LCR consisting of HS3.

16. (Twice amended) The pair of vectors of claim 12 wherein the component of an LCR is a component of the β -globin LCR selected from the group consisting of HS3 and HS4, or a combination thereof.

REMARKS

This paper is filed in response to the Office Action dated March 15, 2000.

Claims 1-22, 23 and 25 are pending. Claims 5, 14, and 16 have been amended to more clearly define the invention. No new matter has been added. In view of the foregoing amendments and arguments that follow, Applicants respectfully request reconsideration of the rejections.

35 U.S.C. § 112, 2nd paragraph

Claims 5, 14, 16 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as indefinite for failing to particularly point out and distinctly claim the invention. The claims have been amended to more clearly define the invention. Accordingly, the rejection should be withdrawn.

35 U.S.C. § 103 (a)

Claims 1-3, 5-14, and 16-21 stand rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over Yates et al., Sadelain et al., Greaves et al., Grosveld et al., Ustav et al., and Svensson et al. Applicants respectfully traverse the rejection. The Office Action fails to establish a *prima facie* case of obviousness as there is no evidence of motivation to combine any of the above cited references to yield Applicants' invention. Significantly, none of the cited references teaches or suggests the use of episomal vectors comprising LCRs. Accordingly, Applicants respectfully request withdrawal of the rejection.

Although the Office Action asserts that the Sadelain reference provides the motivation to

combine the cited references to yield Applicants' invention, Applicants respectfully disagree. The Sadelain reference is directed to retroviral vectors comprising β -globin locus control regions (LCRs) that are useful for gene transfer. Sadelain et al. discuss previous studies conducted with vectors comprising LCRs wherein the studies suggest that the LCR confers position-independent expression of integrated material when the LCRs are present at more than one copy per cell. See column 2, page 6731. Sadelain et al. studied the issue of position independence under conditions where one copy of the transcription unit per cell is integrated in a precise reproducible way. The results obtained by Sadelain et al. indicated that the LCR may not truly confer position-independent expression when present at one copy per cell as it does when present at more than one copy per cell. Sadelain et al. recognized that the data obtained "strongly suggests that it is important to carefully reevaluate the characteristics of larger LCR containing sequences *in the context of single-copy insertions*." See page 6732 (emphasis supplied.)

Although the Office Action suggests that the skilled artisan would thus recognize that "episomal vectors could be used to overcome the problems pointed to by Sadelain et al. because episomal vectors are present at more than one copy per cell and do not integrate into the host chromosome, thereby eliminating position effects," Applicants respectfully disagree. The modification proposed by the Office Action does not solve the problem recognized by Sadelain et al. The problem presented by Sadelain *et al.* might motivate one skilled in the art to try to eliminate position effects *in the context of single-copy insertions*, but this would not direct the art skilled artisan to episomal vectors, as episomal vectors are not integrated. Indeed, assuming, arguendo, that the skilled artisan would be motivated to achieve multiple copies of the vector, he/she would not be directed to episomal vectors but, rather, the vectors used in the Sadelain reference, noting the successful position-independent integration that was referred to in Sadelain.

The Office Action seems to suggest that, based on a combination of the cited references, the use of LCRs in episomal vectors would be an obvious choice to confer position-independence because episomal vectors are present at more than one copy per cell. The idea of using an LCR in an episomal vector to avoid positional effects, however, would not have been considered by those skilled in the art -- the purpose of the LCR was to overcome position effects by opening up the chromatin structure. For example, U.S. Pat. No. 5,532,143 (the '143 patent) states that:

It is hypothesized that the dominant activator sequences [now referred to as LCRs] of the invention may open the chromatin structure of the DNA, making it more accessible and thus may act as a locus organizer.

See, column 4, lines 29-32. Further, LCRs were used to confer "integration site independent, copy number dependent expression when **integrated** into the genome of a host cell." (*See*, column 4, lines 19-21 of the '143 patent, *emphasis supplied*.) As episomal vectors do not integrate, without the hindsight provided by the present invention, one skilled in the art would not have been motivated to combine the cited references to incorporate LCRs in such episomal vectors. Therefore, Applicants respectfully request withdrawal of the rejection.

Claim 23 stands rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over the references cited above as applied to claims 1-3, 5-14, and 16-21, further in view of Chapman et al. However, as discussed above, there has been no motivation established for the obviousness rejection of claims 1-3, 5-14, and 16-21. The Chapman reference is relied upon for the transfection of cultured cells. Chapman et al., however, does not disclose or suggest the use of an LCR in an episomal vector. As the Chapman reference fails to remedy the deficiencies of the above-discussed art, Applicants respectfully request withdrawal of the rejection.

Claim 25 was rejected as allegedly unpatentable over the references cited for claim 23. Applicants respectfully traverse this rejection.

The deficiencies of the references cited for claims 1-3, 5-14, and 16-21 are discussed above. The Chapman reference is relied upon for disclosing the effect of intron A from human cytomegalovirus immediate early gene on heterologous expression in mammalian cells. At most, Chapman et al. describes testing a regulatory element not **candidate** regulatory elements in general. As the Chapman reference fails to remedy the deficiencies of the previously discussed cited art, Applicants respectfully request withdrawal of the rejection.

Applicants believe that the present claims are now in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted

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